TABLE I

THERMODYNAMIC DATA FOR THE REACTION: CYCLOHEXANE (liq., 25°) ⟶ METHYLCYCLOPENTANE (liq., 25°)

	Calcd. from equil. meas.	Calcd. from Parks and Huffman	Calcd. by Moore and Parks
ΔH, cal.	3510	−1100	3930
ΔS, e. u.	7.9	10.0	10.0
$\Delta F°$, cal.	1150	−4100	950

In view of this situation we recently included these two substances in an extensive and very precise investigation of the heats of combustion of organic compounds which is in progress in this Laboratory. We have now obtained the following values, in terms of the "defined" calorie, for the heats of combustion of the liquid hydrocarbons per gram (*in vacuo*) at 25° and 1 atm. constant pressure: cyclohexane, 11,126.7 (±2.1) cal.; methylcyclopentane, 11,173.4 (±3.6) cal. From these data we find for the cyclohexane–methylcyclopentane isomerization $\Delta H_{298.16} = 46.7$ (±4.2) cal. per gram or 3930 (±350) cal. per mole. Taking $\Delta S = 10.0$ (±0.8) e. u. and using the relation $\Delta F = \Delta H - T\Delta S$, we next obtain $\Delta F°_{298.16} = 950$ (±420) cal. per mole. This new third law value for the free energy of isomerization is thus in good agreement with that derived from the equilibrium study of Glasebrook and Lovell.

The new thermodynamic data are now recorded in Column 4 of the table. They serve to emphasize the necessity of very precise combustion data in any accurate free energy calculations based on the third law.

Before concluding, we wish to thank the Shell Development Company for the preparation of extremely pure samples of these hydrocarbons and for the financial support which made this study possible.

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RECEIVED JULY 31, 1939

SYNTHESIS OF 2-METHYL-3-β-HYDROXY-ETHYL-N-[(2-METHYL-6-AMINOPYRIMIDYL-(5))-METHYL]-PYRIDINIUM BROMIDE HYDROBROMIDE

Sir:

In view of the marked specificity of thiamin with respect to the loading of the heterocyclic rings, it seemed of interest to synthesize the isosteric 2-methyl-3-β-hydroxy-ethyl-N-[(2-methyl-6-aminopyrimidyl-(5))-methyl]-pyridinium bromide hydrobromide. This has been accomplished in ten steps, starting with 6-amino-3-nitro-2-picoline [Seide, *J. Russ. Phys.-Chem. Soc.*, **50,** 542 (1920)]. This was converted into the 6-hydroxy-3-nitro-2-picoline according to the method of Seide (*ibid.*, p. 540). From the hydroxy compound the 6-chloro-3-nitro-2-picoline was obtained by treatment with phosphorus pentachloride. Chlorine was eliminated and the nitro group simultaneously reduced to the amino group with hydrogen and a palladium catalyst [Binz and von Schickh, *Ber.*, **68,** 320 (1935)]. The 3-amino-2-picoline (m. p. 113°) was converted into the corresponding nitrile (m. p. 58°) by a Sandmeyer reaction at *p*H 4.5. The nitrile was converted into the 2-picolyl methyl ketone (b. p. 75–78°, 2 mm.) by a modified LaForge procedure [THIS JOURNAL, **50,** 2480 (1928)]. The ketone was brominated, the reaction product without isolation being converted into the acetyl derivative by treatment with potassium acetate in alcohol. The acetylated ketol was reduced without isolating it to 2-methyl-3-β-hydroxyethylpyridine (b. p. 125°, 3 mm.), picrate (m. p. 125°). (*Anal.* Calcd. for $C_{14}H_{14}O_8N_4$: C, 45.95; H, 3.81; N, 15.3. Found: C, 46.04; H, 3.66; N, 15.37). This compound was acetylated using the method described by Kuhn [*Z. physiol. Chem.*, **259,** 50–51 (1939)] (b. p. 90–92°, 3 mm.). (*Anal.* Calcd. for $C_{10}H_{13}O_2N$: N, 7.82; CH_3CO, 24.02. Found: N, 7.9; CH_3CO, 24.4, 24.2.) The β-hydroxyethyl derivative was condensed with 2-methyl-5-bromomethyl-6-aminopyrimidine hydrobromide [THIS JOURNAL, **59,** 1052 (1937)] and the 2-methyl-3-β-hydroxyethyl-N-[(2-methyl-6-aminopyrimidyl-(5))-methyl]-pyridinium bromide hydrobromide (m. p. 247°) was obtained. (*Anal.* Calcd. for $C_{14}H_{20}ON_4Br$: C, 40.00; H, 4.76; N, 13.33; Br, 38.09. Found: C, 39.72; H, 4.97; N, 13.83; Br, 37.75.)

Owing to the difference between the pyridine and thiazole rings, the new derivative permits synthesis of isomers not possible for a thiazole and, therefore, the corresponding 2-methyl-5-β-hydroxyethyl-N-[(2-methyl-6-aminopyrimidyl-(5))-methyl]-pyridinium bromide hydrobromide (m. p. 245°?) was synthesized in a similar manner starting from the corresponding ketone [*Ber.*, **57,** 832 (1924)]. The 2-methyl-5-β-hydroxyethylpyridine is a low melting solid (b.p. 103°, 2 mm.). (*Anal.* Calcd. for $C_8H_{11}ON$: C, 70.00; H, 8.03; N, 10.21. Found: C, 69.60; H, 7.77; N, 10.08.)

A detailed report of our work will be presented in the future.

We acknowledge gratefully valuable suggestions of Dr. H. Gilman and Dr. F. B. LaForge. We are also indebted to Merck & Co., Inc., for generously furnishing us with a supply of the pyrimidine derivative used in this work. The analytical work was carried out by Dr. Carl Tiedcke of New York City.

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RECEIVED JULY 3, 1939

VITAMIN K POTENCIES OF SYNTHETIC COMPOUNDS

Sir:

In view of the failure of the absorption of many patients in which vitamin K therapy is highly desirable, we have been examining various compounds which could be administered intravenously in aqueous solution. The most active compound found is 1,4-dihydroxy-2-methylnaphthalene which has a potency of approximately 1000 Thayer–Doisy units per milligram. It can be prepared readily by the reduction of the highly potent 2-methyl-1,4-naphthoquinone. Since this preparation is soluble in dilute alkali and has a high degree of potency (approximately equal to the potency of 2-methyl-1,4-naphthoquinone), it seems that this compound may prove very important for intravenous vitamin K therapy.

Supplementing our previous preliminary report [THIS JOURNAL, **61**, 1932 (1939)], we have reassayed several quinones to determine their optimum potency values. Except for 2-methyl-1,4-naphthoquinone, these more recent data agree with our previous findings. The assay of this compound was carried out by the Thayer–Doisy method, making a concurrent test, at six, eighteen and seventy-two hours. The standard was also run at varying levels at the same time for each series. The data are given in Table I. The details as to the method of feeding, care of the chicks, length of test period, manner of bleeding, etc., were essentially the same as described previously.

TABLE I

Assay period	Thayer–Doisy units per mg.
6 hours	1110
18 hours	970
72 hours	1070
Average	**1050**

The potency of 2-methyl-1,4-naphthoquinone (Thayer–Doisy units) agrees with the value previously assigned to the natural K_1, namely, 1000 units per milligram [*Proc. Soc. Exp. Biol. Med.*, **41**, 194 (1939)]. These results also confirm the findings of Ansbacher and Fernholz [THIS JOURNAL, **61**, 1932 (1939)].

Incidentally, in view of these observations and the lack at this time of a suitable standard, it is suggested that 2-methyl-1,4-naphthoquinone should be adopted as a basic standard for the assay of vitamin K. This compound has the desirable qualities of a standard in that it can be obtained readily in a satisfactory state of purity, has a definite melting point for characterization, and when protected from excessive exposure to light is relatively stable. The unit could then be defined in the terms used by the League of Nations committee as the specific vitamin K activity of one microgram of pure 2-methyl-1,4-naphthoquinone.

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RECEIVED AUGUST 21, 1939

ANTIHEMORRHAGIC ACTIVITY OF SIMPLE COMPOUNDS

Sir:

In connection with our investigation of vitamin K, we have tested recently a large number of derivatives of α-naphthoquinone, many of which have been prepared and reported by Professor Fieser and his collaborators[1] and some of which were synthesized in this Laboratory. At this time we wish to report our findings of the antihemorrhagic activity of 2-methyl-1,4-naphthoquinone and of some other related substances of significance.

One of the first quinones we assayed was 2-methylnaphthoquinone and, because it did not appear at that time to be as active as 2,3-dimethyl-1,4-naphthoquinone,[1] we did not determine its minimum dose.

Following the appearance of the extremely interesting report of Ansbacher and Fernholz,[2] we reinvestigated the activity of 2-methyl-1,4-naphthoquinone, and we are now in complete agreement with them.

(1) Fieser, *et al.*, THIS JOURNAL, **61**, 1925, 1926, 2206 (1939).
(2) Ansbacher and Fernholz, *ibid.*, **61**, 1924 (1939).